American Journal of Medical Genetics 69:225–228 (1997)

Classifying Sex Biased Congenital Anomalies

Mark S. Lubinsky*
Department of Pediatrics, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee

The reasons for sex biases in congenital anomalies that arise before structural or hormonal dimorphisms are established has long been unclear. A review of such disorders shows that patterning and tissue anomalies are female biased, and structural findings are more common in males. This suggests different gender dependent susceptibilities to developmental disturbances, with female vulnerabilities focused on early blastogenesis/determination, while males are more likely to involve later organogenesis/morphogenesis. A dual origin for some anomalies explains paradoxical reductions of sex biases with greater severity (i.e., multiple rather than single malformations), presumably as more severe events increase the involvement of an otherwise minor process with opposite biases to those of the primary mechanism. The cause for these sex differences is unknown, but early dimorphisms, such as differences in growth or presence of H-Y antigen, may be responsible. This model provides a useful rationale for understanding and classifying sex-biased congenital anomalies. Am. J. Med. Genet. 69:225–228, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: blastogenesis; congenital anomaly; determination; female sex; male sex; morphogenesis; organogenesis

INTRODUCTION

Many congenital anomalies have sex biases. Some reflect structural or hormonal differences, such as male urethral stenosis [Pagon et al., 1979], or pyloric hypertrophy from testosterone [Arena and Smith, 1978]. However, many arise before such dimorphisms occur and are difficult to explain.

Arena and Smith [1978] categorized findings by organ system or anatomical region and found male excesses except for the nervous system. While noting a possible role for selective early fetal mortality, they suggested instead effects of X and/or Y linked genes in morphogenesis that extended beyond the development of sex related structures.

Unfortunately, all these hypotheses are unsatisfactory: 1) Selective early mortality begs the question: with biases for both sexes, why are some defects male lethal and others female? 2) X or Y linkage patterns for these anomalies do not seem overly common, and most are sporadic. 3) Female biased anomalies occur outside the nervous system (Table I).

Recent work on neural tube defect biases has led to some additional explanations, but these are debatable [cf. Brook et al., 1994], leaving this question still open. Here, Arena and Smith's survey [1978] is extended to reinvestigate this issue.

METHODS

Congenital anomalies reviewed by Arena and Smith [1978], plus other findings, especially of tissue or pattern, were listed by ratios of males to total cases (Table I). Spina bifida was divided into neural tube defects type 1 and 5 [Van Allen et al., 1993]. Cancers and anomalies arising late in development (e.g., hemangiomas), or related to known sexual dimorphisms (including anal/rectal atresia and agenesis), were omitted.

RESULTS (TABLE I)

While origins of anomalies are not always clear, female and male biases seem to involve different types of findings:

1. Females show tissue anomalies (teratomas, lipomas, and perhaps hypoplastic left heart) and duplications (conjoined twins, diplomyelia, stomach, face, and rectum) that suggest early problems at the stage of blastogenesis [Opitz, 1993], probably with establishment of pattern and tissue type during the process of determination [Bryant et al., 1981].

2. Males have more organ specific findings, often involving cell movement, as with cardiac rotations (tetralogy of Fallot and transposition), neural crest cell migration (Hirschsprung disease and perhaps truncus arteriosus and aortic valve anomalies [Miyabara et al., 1989]), and renal ectopias, more typical of later morphogenic events during the stage of organogenesis.

Gastric teratoma is a notable exception as an almost exclusively male tissue finding, but skewing is so ex-

*Correspondence to: Mark Lubinsky, M.D., Genetics Center, Children's Hospital of Wisconsin, P.O. Box 1997, Mail Station 716, Milwaukee, WI 53201.

Received 14 February 1995; Accepted 31 October 1995

TABLE I. Sex Ratios of Early Developmental Anomalies

Malformation	Males/Total	Reference
Sacrococcygeal teratoma	.25	Bale [1984]
Diplomyelia without meningomyelocele	.26	Sheptak [1978] Matson [1969]
Alobar holoprosencephaly	.26	Arena and Smith [1978]
Occipital encephalocele	.27	Arena and Smith [1978]
Duplication, stomach	.31	Bartels [1967] Kremer et al. [1970]
Duplication, rectum	.31	Smith and Stephens [1988]
Hypoplastic left heart	.32	Arena and Smith [1978]
Duplication of face	.33	Barr [1982]
Midline lipoma	.33	Bale [1984]
Anencephaly	.34	Arena and Smith [1978]
Neural tube defect type 1	.36	Cuckle et al. [1993]
Conjoined twins	.37	Edmonds and Layde [1985]
Duplication of ureter	.38	Editorial [1988]
Atrial septal defect	.38	Arena and Smith [1978]
Cleft palate	.45	Arena and Smith [1978]
Single umbilical artery	.46	Heifitz [1984]
Neural tube defect type 5	.49	Cuckle et al. [1993]
Anotia/microtia	.53	Hook et al. [1976]
Omphalocele	.55	Arena and Smith [1978]
Preauricular tags	.58	Conway and Wagner [1965]
Tetralogy of Fallot	.58	Arena and Smith [1978]
Branchial clefts	.60	Conway and Wagner [1965]
Crossed renal ectopia	.60	McDonald and McClellan [1957]
Truncus arteriosus	.62	Arena and Smith [1978]
Tracheal-esophageal fistula	.62	Depaepe et al. [1993]
Cleft lip	.63	Arena and Smith [1978]
Syndactyly of hand	.64	Arena and Smith [1978]
Diaphragmatic hernia	.65	Arena and Smith [1978]
Bladder exstrophy	.70	Arena and Smith [1978]
Coarctation of aorta	.70	Arena and Smith [1978]
Cleft lip and palate	.71	Arena and Smith [1978]
Poland complex	.71	Arena and Smith [1978]
Great vessel transposition	.72	Arena and Smith [1978]
Bilateral renal agenesis	.72	Arena and Smith [1978]
Sirenomelia	.73	Arena and Smith [1978]
VACTERL association	.74	Khoury et al. [1983] Czeizel and Ludanyi [1985]
Pericardial defects	.75	St. Pierre and Froment [1970]
Aortic valve anomalies	.76	Arena and Smith [1978]
Meckel diverticulum	.77	Arena and Smith [1978]
Hirschsprung disease	.79	Passarge [1967]
Gastric teratoma	.95	Senocak et al. [1990]

treme [Senocak et al., 1990] that hormonal influences are likely.

DISCUSSION

Congenital anomaly epidemiology is complex: one finding can have several causes, or one cause several findings, populations may differ in time or space, and biases of ascertainment are common. Statistical tests are therefore omitted because they imply data quality that may not exist.

Still, trends seem clear: of the 14 most female biased anomalies in Table I, at least 8 involve pattern or tissue findings of early origin that, except for gastric teratoma, are absent with male biases. Overall, sex-dependent developmental vulnerabilities explain multiple observations of sex biases in ways that selective mortality, X or Y linkage, and anatomic specificity do not.

Identification of specific processes is difficult: both blastogenesis and determination are early and overlap, as do later morphogenesis and organogenesis. However, some blastogenic anomalies (e.g., tracheo-esophageal defects and diaphragmatic hernia [Opitz, 1993]) are male biased (Table I), pointing more towards determination.

Teratomas and lipomas have a predilection for the midline, which may be particularly vulnerable to problems with determination [Lubinsky, 1987]. Assignments to this area can be difficult [Khoury et al., 1989], but several likely candidates (holoprosencephaly, encephalocele, anencephaly, type 1 neural tube defects, and cleft palate) are female biased. Midline anomalies with male biases should involve mechanisms other than determination, and canalization has been suggested for male biased type 5 neural tube defects [Seller, 1987, 1995].

The type of process is central here. Thus, for gut duplications, lower "side by side" female biased cases often involve replications of other posterior structures, while generally male biased (save for the duodenum)

cystic tubular duplications (dorsal enteric remnants) associate instead with vertebral and other structural anomalies [Skandalakis and Gray, 1994, pp 225–230, 249–250].

Some findings, such as organ hypoplasias, may have complex and heterogeneous origins potentially involving both male and female biased processes. This is supported by decreased sex biases with added anomalies with anencephaly, spina bifida, encephalocele [Khoury et al., 1982; Hall, 1986; Martinez-Frias et al., 1986; Seller, 1987; Hall et al., 1988; Rodriguez et al., 1992], single umbilical artery [Heifitz, 1984], and diaphragmatic hernia [Torfs et al., 1992]. A decreased bias with greater severity is hard to explain with a single process, but with dual origins, "strong" events could increase the involvement of otherwise minor second processes with opposite biases from the primary disturbance.

Very early sex differences may have a role: Seller [1987, 1995] linked differential early growth rates to neural tube defects but, despite earlier male maturity, Brook et al. [1994] failed to find this in a mouse model. Anomalous X inactivation may also be involved here [Hall, 1986; James, 1988] but does not explain male biases in other anomalies.

Although females tend to be smaller than males, some anomalies associated with small size, such as VATER and tracheoesophageal fistula [Chen, 1979; Czeizel and Ludanyi, 1985; Khoury et al., 1983; Depaepe, 1993], are male biased, making size an independent sex associated risk factor and not a cause of sex biases.

H-Y antigen is a cell surface marker limited to males. A diffusable form produced by fetal testes [Wachtel, 1983] could increase stability for males by providing a gradient with positional information for determination [Bryant et al., 1981]. Also, its presence as a surface marker could slightly reduce available space for cell adhesion molecules important in morphogenesis [Edelman, 1985], marginally weakening males compared to females with more adhesion molecules per cell. This is speculative but does suggest a way in which dual effects could arise from a single factor.

CONCLUSIONS

Sex biases of early developmental anomalies reflect differential vulnerabilities of specific processes. Males have more late structural/morphogenetic findings; females have more early blastogenetic/determinative tissue, patterning, and midline anomalies. When findings involve both processes, greater severity may actually decrease sex biases. The reasons for these different vulnerabilities is unknown.

REFERENCES

Arena JFP, Smith DW (1978): Sex liability to single structural defects. Am J Dis Child 132:970–972.

Bale PM (1984): Sacrococcygeal developmental abnormalities and tumors in children. Perspect Pediatr Pathol 1:9–56.

Barr M (1982): Facial duplication: Case, review, and embryology. Teratology 25:153–159.

Bartels RJ (1967): Duplication of the stomach: Case report and review of the literature. Am Surg 33:747–752.

Brook FA, Estiberio JP, Copp AJ (1994): Female predisposition to cranial neural tube defects is not because of a difference between the sexes in the rate of embryonic growth or development during neurulation. J Med Genet 31:383–387.

Bryant SV, French V, Bryant PJ (1981): Distal regeneration and symmetry. Science 212:993–1002.

Chen H, Goei GS, Hertzler JH (19xx): Family studies on esophageal atresia with or without tracheoesophageal fistula. New York: Alan R. Liss, Inc., for the National Foundation—March of Dimes. BD:OAS XV (5C): 117–144.

Conway H, Wagner KJ (1965): Congenital anomalies of the head and neck as reported on birth certificates in New York City, 1952 to 1962 (inclusive). Plast Reconstr Surg 36:71–79.

Cuckle HS, Wald NJ, Althouse R (1993): Sex differences in the location of a spina bifida lesion. J Med Genet 30:262–263.

Czeizel A, Ludanyi I (1985): An aetiological study of the VACTERL-association. Eur J Pediatr 144:331–337.

Depaepe A, Dolk H, Lechat MF (1993): The epidemiology of tracheo-oesophageal fistula and oesophageal atresia in Europe. EUROCAT Working Group. Arch Dis Childh 68:743–748.

Edelman GM (1985): Cell adhesion molecule expression and the regulation of morphogenesis. Cold Spring Harbor Symp Quant Biol 50:877–889.

Editorial (1988): Duplex ureter. Lancet i:515.

Edmonds LD, Layde PM (1985): Conjoined twins in the United States 1970–77. Teratology 25:301–308.

Hall JG (1986): Neural tube defects, sex ratios, and X inactivation. Lancet ii:1334.

Hall JG, Friedman JM, Kenna BA, Popkin J, Jawanda M, Arnold W (1988): Clinical, genetic, and epidemiological factors in neural tube defects. Am J Hum Genet 43:827–837.

Heifitz S (1984): Single umbilical artery: A statistical analysis of 23 autopsy cases and review of the literature. Perspect Pediatr Pathol 8:345–379.

Hook EB, Marden PM, Reiss NP, Smith DW (1976): Some aspects of the epidemiology of human minor birth defects and morphological varients in a completely ascertained newborn population (Madison Study). Teratology 13:47–55.

James WH (1988): Anomalous X inactivation: The link between female zygotes, monozygotic twinning, and neural tube defects. J Med Genet 25:213–215.

Khoury MJ, Cordero JF, Greenberg F, James LM, Erickson JD (1983): A population study of the VACTERL association: Evidence for its etiologic heterogeneity. Pediatr 71:815–820.

Khoury MJ, Cordero JF, Mulinare J, Opitz JM (1989): Selected midline defect association: A population study. Pediatrics 84:266–272.

Khoury MJ, Erickson JD, James LM (1982): Etiologic heterogeneity of neural tube defects: Clues from epidemiology. Am J Epidemiol 115: 538–548.

Kremer RM, Lepoff RB, Izant RJ Jr (1970): Duplication of the stomach. J Pediatr Surg 5:360–364.

Lubinsky MS (1987): Midline developmental "weakness" as a consequence of determinative field properties. Am J Med Genet Suppl 3:23–28.

Martinez-Frias ML, Parralo JA, Salvador J, Frias JL (1986): Sex ratios in neural tube defects. Lancet ii:871–872.

Matson DD (1969): "Neurosurgery of Infancy and Childhood." Springfield, IL.: Charles C Thomas

McDonald JH, McClellan DS (1957): Crossed renal ectopia. Am J Surg 93:995–1002.

Miyabara S, Sugihara H, Maehara N, et al (1989): Significance of cardiovascular malformations in cystic hygroma: A new interpretation of the pathogenesis. Am J Med Genet 34:489–501.

Opitz JM (1993): Blastogenesis and the "primary field" in human development. BD:OAS 29(1):3–37.

Pagon RA, Smith DW, Shephard TH (1979): Urethral obstruction malformation complex: A cause of abdominal muscle deficiency and "prune belly." J Pediatr 94:900–906.

Passarge E (1967): The genetics of Hirschsprung's disease. NEJM 276:138–143.

Rodriguez JI, Rodriguez-Peralto JL, Muro M, Urioste M, Palacios J (1992): Anencephaly and limb deficiencies. Am J Med Genet 44:66–71.

Seller MJ (1987): Neural tube defects and sex ratios. Am J Med Genet 26:699–707.

Seller MJ (1995): Sex, neural tube defects and multisite closure of the human neural tube. Am J Med Genet 58:332–336.

Senocak ME, Kale G, Buyukpamukcu N, Hicsonmez A, Caglar M (1990): Gastric teratoma in children including the third reported female case. J Pediatr Surg 25:681–684.

St. Pierre A, Froment R (1970): Absenses totales et partiales du pericarde. Arch Mal Coeur 63:638–657.

Sheptak PE. Diastemalomelia-diplomyelia. In PJ Vinken, GW Bruyn (eds.): "Handbook of Clinical Neurology, Vol. 32: Congenital Malformations of the Spine and Spinal Cord." Amsterdam: North-Holland Publishing Co, pp 239–254.

Skandalakis JE, Gray SW (1994): "Embryology for Surgeons. The Embryological Basis for the Treatment of Congenital Defects," 2nd ED. Baltimore: Williams and Wilkins.

Smith ED, Stephens FD (1988): Duplication and vesicointestinal fissure. BD:OAS 24(4):551–580.

Torfs CP, Curry CJ, Bateson TF, Honore LH (1992): A population-based study of congenital diaphragmatic hernia. Teratology 46:555–565.

Van Allen MI, Kalousek DK, Chernoff GF et al (1993): Evidence for multisite closure of the neural tube in humans. Am J Med Genet 47:723–743.

Wachtel SS (1983): "The Biology of Sex Determination." New York: Grune and Stratton.